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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,712	11/09/2001	Ronald K Schcule	GA0206C	6542

EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

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GENZYME CORPORATION
LEGAL DEPARTMENT
15 PLEASANT ST CONNECTOR
FRAMINGHAM, MA 01701-9322

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	09/890,712	SCHEULE ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

2) ☐ Notice of References Cited (PTO-892)

3) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

4) ☐ Interview Summary (PTO-413) Paper No(s). _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other:

☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *82/01*.

Claims 1-21 are pending.

Applicant's species election without traverse of intravenous injection administration in the response filed 10/06/03 is acknowledged.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling:

1/ A method of generating an anti-tumor cell immune response in a tumor bearing mammal comprising the step of administering to said tumor bearing mammal a composition comprising a complex, said complex comprising:

a cationic molecule and an immunologically active nucleic acid sequence without an expressible cDNA insert, wherein the nucleic acid sequence contains at least one immunologically active CpG motif, and wherein said composition is administered in an amount effective to stimulate said anti-tumor cell immune response;

2/ A method of prolonging the survival of a tumor bearing mammal comprising the step of

administering to said tumor bearing mammal a composition comprising a complex, said complex comprising:

a cationic lipid molecule and an immunologically active CpG motif containing nucleic acid sequence, wherein said complex is provided in an amount effective to stimulate a protective anti-tumor cell immune response, thereby prolonging the survival of the tumor bearing mammal, and wherein said cationic molecule is the compound GL-67.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

1/ Issue regarding the use of a non-CpG containing nucleic acid sequence as an immunologically active sequence

The specification (pages 2, second par., third par., page 3, second par.) coupled with the prior art of record teach that non-expressible nucleic acid sequences are immunogenic when having a CpG motif contained therein. On the basis of Example 7, the specification further contemplates that other immunostimulatory motifs in addition those harboring the consensus 5'-RRCGYY-3' are necessary to stimulate the desire inflammatory response (a subset of the "immune response", indicative by an increased levels of TNF-alpha, INF-γ, IL-

6, and IL-12). However, the specification does not teach as to what are exactly the structures or common structure of those non-CpG immunostimulatory motifs, nor does the example 7 addresses the fact that the employed nucleic acid sequence in example 7 still contains at least one immunologically active CpG motif. Furthermore, the state of the prior art exemplified by McCluskie *et al.* (The J. of Immunology, 161, pp. 4463-4466, 1998) teaches (p. 4465, column 1):

> Results were due to the CpG motif rather than to a nonspecific effect of the ODN backbone, since mice immunized with 1 ug of HbsAg plus 10 ug of non-CpG ODNs had no (7 out of 10) or very low (3 of 10) titers of anti-HBs IgG Abs.

McCluskie *et al.* (The J. of Immunology, 161, pp. 4463-4466, 1998) also teaches (page 4465, column 1, third paragraph) that "no IgA was detected in the lung washes with 1-ug dose of non-CpG ODN/CT" .

Thus, given that the precise common structure by which a non-CpG DNA mediates either an immune-stimulatory effect so as to generate a therapeutic or protective anti-tumor effect is not completely understood, and that the exemplified results can not be reasonably extrapolated to a particular structure(s) or common structures of non-CpG containing immunologically reactive DNA, which are essential for the making and use of the claimed invention as contemplated by applicants, it is not apparent how a skilled artisan, without any

undue experimentation, practices the claimed invention drawn to a cancer treatment by using an immunologically non-CpG motif containing nucleic acid sequence.

2/ Issue regarding the use of a generic cationic molecule (defined as a cationic polymer, cationic amphiphile, or cationic lipid), which is not necessarily a cationic lipid compound.

The claims as written are reasonably being interpreted as embracing non-lipid cationic molecules. The specification as a whole only teaches and provides sufficient guidance for the making and use of a complex comprising a cationic lipid compound and an immunologically active CpG motif containing nucleic acid sequence. However, the claims are not necessarily limited to such complexes wherein a cationic lipid compound is employed. In fact, the specification teaches as a whole that the presence of both a CpG motif containing nucleic acid sequence and a cationic lipid compound is essential for the efficacy in generating an anti-tumor immune response. While it is generally understood in the art of record that cationic amphiphiles, cationic lipids, and cationic polymers have been used to enhance the delivery, stability and therapeutic efficacy of an expressible DNA molecule or a non-expressible CpG motif containing DNA, the state of the art of record is silent as to an interchangeable use of such a cationic molecule as a non-expressible DNA vaccine complex in a cancer prevention treatment in an individual. In fact, cationic lipids compounds are structurally distinct and are expected to behave unpredictably in an *in vivo* environment. The specification focuses mainly on cationic amphiphiles or cationic lipids, and all of its working examples involve the use of one particular lipid compound, the GL-67. Filion (International J. of Pharmaceutics, 162:159-170, 1996), states:

[t]The use of cationic liposomes to target DNA to the gastrointestinal tract is inappropriate. Cationic DOPE/DOTAP liposomes are extremely toxic to CD1 mice following the administration of a single dose, provoking a profound and lethal hypothermia.

Complementary to our results, we have identified a range of adverse effects associated with the use of cationic lipids or cationic liposome (Table 2). This non-exhaustive list demonstrates very clearly that cationic liposomes must be used with caution for DNA (or drug) delivery. We believe that alternatives to cationic liposomes for DNA therapy should be considered in order to avoid these dose-limiting and often fatal adverse effect (page 169, column 1).

These results, in addition to the observation that cationic liposomes are extremely toxic following oral administration, indicate that DOPE/cationic lipid liposomes are not appropriate for DNA (or drug) delivery (abstract).

As such, with respect to claim 7, 18, and claims dependent there from the claimed invention is only reasonably enabling for claims that claim specifically:

A method of prolonging the survival of a tumor bearing mammal comprising the step of

A method of generating an anti-tumor cell immune response in a tumor bearing mammal comprising the step of administering to said tumor bearing mammal a composition comprising a complex, said complex comprising:

a cationic lipid molecule and an immunologically active CpG containing nucleic acid sequence, wherein said complex is provided in an amount effective to stimulate a protective

anti-tumor cell immune response, thereby prolonging the survival of the tumor bearing mammal, and wherein said cationic molecule is the compound GL-67.

3/ Issue regarding claims drawn to a method of generating a protective anti-tumor response in a mammal including primates such as subjects at risk of developing a cancer.

The specification contemplates, for example, on page 4 bridging page 5 that a protective anti-tumor response is a protective anti-tumor response that may provide long term protective immune memory. The specification does not provide any closed definition as to what is meant by the "long term protective immune response" As such, and in view of the customary and ordinary meaning of the "long term protective immune memory" in the art, the claimed invention as claimed in claim 7 and claims dependent there from would embrace a method of preventing a mammal such as primates including non-tumor bearing humans, domestic mammals, and farmed mammals from developing or having a tumor or cancer. The types of tumor or cancer are not limited in the claimed invention and may embrace melanoma, breast tumor, ovarian tumor, pancreatic tumor, colon tumor, brain tumor, liver tumor, leukeumia, and stomach tumor. The state of the prior art exemplified by Filion or McCluskie *et al.* not only does not teach or even suggest that it is routine or conventional in the art to employ any form of DNA complex as a cancer vaccine so as to provide a protective anti-cancer effect to an non-tumor bearing individual, but also suggests that while it may be conventional in the prior art to employ a CpG motif contaiing DNA to treat therapeutically a tumor bearing mammal, notably in the form of increasing a Th1 immune resposne or cytokine induced inflammatory response in small animals such as mice or rats,

the state of the art of DNA cancer vaccine remains reasonably unpredictable at the time the invention was made. More specifically,

McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) teaches that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in nun-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees..., and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs). In addition, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, antigens" (page 296, column 1), and that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen" (page 297, column 1).

Lee *et al.,* Critical Reviews in Therapeutic Drug Carrier System, 14, 2:173-206, 1997, states:

> Because gene transfer efficiency is determined by a large number of factors, many of which are not well understood, it is difficult to predict the performance of a specific

cationic liposome formulation based simply on the cationic lipid structure and/or the lipid composition. The gene transfer property of a vector is determined by 1) particle (DNA/lipid) size; 2) lipid composition; 3) lipid/DNA ratio; 4) formulation procedure; 5) DNA concentration; 6/ strength and tissue specificity of the promoter and enhancer elements; 7) for *in vitro* gene delivery, cell line, duration of transfection, cell confluency level, presence or absence of serum, etc; For *in vivo* delivery, route of administration (page 184);

While the strength and tissue specificity of the promoter and enhancer elements are not required for the claimed invention wherein a non-expressible DNA is employed as an immunologically active DNA as one of the main components in a cationic lipid/DNA complex, the state of the prior art does suggest and teaches that the *in vivo* behaviors and/or activities of one particular or other cationic lipid/DNA complexes cannot be reasonably extrapolated from that of another particular cationic lipid/DNA complex.

The specification as a whole provide a number of working examples, which focus mainly on the efficacy of the GL-67/CpG motif containing DNA sequence (expressible or non-expressible) in generating a therapeutically relevant immune response in a number of different tumor established (xenografted) mice and rats. In the mice and rat models, not only the generated immune response appears to be sufficient to inhibit the growth of the xenografted tumors, it is also sufficient to prolong the survival of the treated mice and rats. Coupled with state of the prior art regarding the well-established immunotherapeutic activities of CpG motif containing nucleic acid sequences in inhibiting the growth of a tumor

in a tumor model such as mice or rats, the application is reasonably enabling for claimed embodiments, drawn specifically to a method of generating an anti-tumor cell immune response in a tumor bearing mammal comprising the step of administering to said tumor bearing mammal a composition comprising a complex, said complex comprising:

a cationic lipid molecule and an immunologically active nucleic acid sequence without an expressible cDNA insert, wherein said composition is administered in an amount effective to stimulate said anti-tumor cell immune response;

However, neither the specification nor its working examples provide substantial evidence demonstrating an anti-cancer protective effect in any healthy individual or art-recognized animal model, on which a person skilled in the art could reasonably conclude that a cationic lipid/DNA complex(es), regardless of whether the DNA is expressible or not, is or are effective for use as a master vaccine in preventing any type of cancers or tumors developing in an vaccinated individual. One closest example, example 8, provides an ovarian tumor (MOT) bearing mouse model, in which a generated immune response is sufficient to prolong the survival of the mice against the fist challenge and subsequent challenge of MOT tumor cells, *e.g.*, 2, 9 and 16 days. On the basis of this prolonged survival wherein no particular time period is provided, Applicants then suggest that the result indicates a formulation-dependent generation of a protective, memory-based immune response that was systemic in nature, and that this is sufficient to provide patentability for the broad claimed invention as set forth in claim 7. However, a close review of the working example does indicate the followings: 1/ the prolonged survival period was only measured at most for 16 days, 2/ not only the GL-67/DNA is used as a priming antigen, the subsequent

challenge of the same MOT tumor cells wherein the immune response was already primed specifically against the established MOT tumor cells is not indicative of a protective effect against any formation of an endogenous tumor wherein no specifically primed immune response is present or activated; and 3/ the experiments were employed in an already MOT tumor grafted in mice. Thus, these deficiencies and/or non-correlative factors are not deemed sufficient to lead on skilled in the art to reasonably conclude that the GL-67/DNA complex is effective for use as a DNA vaccine for preventing a formulation of an endogenous ovarian tumor in a tumor-free individual, let alone other claimed embodiments wherein an enormous number of other cationic lipid/DNA complexes are claimed as cancer vaccine(s). At best, the working example 8 coupled with the guidance provided by the as-filed specification provides substantial evidence showing that one skilled in the art not only could use GL-67/CpG containing DNA complex in therapeutically combating the growth of a tumor in a mammal, the complex surprisingly could be used to prolong the survival of a tumor bearing mammal.

To further substantiate unpredictable factors involved in using a particularly type of cationic lipid complex, which has not been shown to provide any anti-cancer protective effect, Filion (International J. of Pharmaceutics, 162:159-170, 1996), states:

[t]The use of cationic liposomes to target DNA to the gastrointestinal tract is inappropriate. Cationic DOPE/DOTAP liposomes are extremely toxic to CD1 mice following the administration of a single dose, provoking a profound and lethal hypothermia.

Complementary to our results, we have identified a range of adverse effects associated with the use of cationic lipids or cationic liposome (Table 2). This non-

exhaustive list demonstrates very clearly that cationic liposomes must be used with caution for DNA (or drug) delivery. We believe that alternatives to cationic liposomes for DNA therapy should be considered in order to avoid these dose-limiting and often fatal adverse effect (page 169, column 1).

These results, in addition to the observation that cationic liposomes are extremely toxic following oral administration, indicate that DOPE/cationic lipid liposomes are not appropriate for DNA (or drug) delivery (abstract).

Notwithstanding the complexities associated with the use of a cationic lipid as a main component in an anti-cancer vaccine, McKenzie, Immunologic Res, 24,3:225-244, 2001, states (page 232, column 1) that "CpG DNA, when added as an adjuvant with a DNA vaccine, gave no further enhancement of CTLs in one study". McKenzie also states on page 232:

There is also another level of complexity for CpG motifs. The optimal motif for stimulation differs between species. CpG motifs can also be immuno-suppressive or neutralizing, depending on the context of flanking residues.

Agrawal, TRENDS in Molecular Medicine, Vol. 8, 3:114-121, 2002, states:

The DNA sequences containing an unmethylated CpG dinucleotide flanked by two purine bases on the 5'-side and two pyrimidine bases on the 3'-side, such as

GACGTT, were found to activate the mouse immune system efficiently. However, the human immune cells responded poorly to this hexameric motif, suggesting that the sequences required for CpG-related immune stimulation varies from species to species (page 114 through page 115).

The pattern and kinetics of induction of the cytokines *in vivo* depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (page 115, last full paragraph).

These unpredictable factors as expressed in the art of record clearly provide substantial evidence showing that the claimed invention as claimed specifically in claim 7 and claims dependent there from is not reasonably enabling to its full breath at the time the invention was made, particularly on the basis of the as-filed application.

Thus, in view of the lack of any established nexus between the guidance provided by the as-filed specification including the *in vivo* data shown in the working examples and the subject matter being sought in the claims, one must evaluate the evidence presented and determine whether applicant has demonstrated such correlation or a reasonable likelihood of such. In the instant case, the data presented in the as-filed specification support a conclusion of unpredictability and lack of reproducibility of the claimed invention as broadly claimed. This conclusion coupled with state of the art, as indicated in the stated Office actions, is consistent with a finding of lack of enablement for the practice of what is claimed. The as-filed application fail to address these art-recognized limitations with regard to the

unpredictability of claiming a full breadth encompassing a generic cationic lipid/DNA complex for use to generate anti-cancer protective responses in an individual at the time the invention was made. Thus, based upon the evidence in the record, which demonstrates that there is a reasonable basis for questioning the assertions regarding the enablement of the claimed invention, it is not apparent as to how a skilled artisan, without any undue experimentation, reasonably extrapolates from the applicant's disclosure including the shown animal model to the entire breadth of the claims. It is not apparent then how one skilled in the art, without undue experimentation, practices the claimed invention, and/or uses a broadly claimed cationic molecule/DNA complex as a DNA cancer vaccine to provide an active and protective immunity against a formulation of a tumor in an individual, let alone a the full scope of a "mammal", particularly on the basis of applicant's disclosure, and in view of the doubts expressed in the art of record at the time the invention was made.

Note that even while one of applicant's cationic lipid/DNA complex exhibits an efficacy in prolonging the survival of the treated rats or mice, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

To the extent that the claimed invention embrace a method of generating a protective anti-tumor cell immune response in a mammal having a tumor, the method comprising the step of administering to a tumor bearing mammal a composition comprising a complex, said complex comprising:

a cationic lipid molecule and an immunologically active nucleic acid sequence without an expressible cDNA insert, wherein said composition is administered in an amount effective to stimulate said protective anti-tumor cell immune response, thereby inhibiting the growth of the tumor,

The following rejections are applicable.

Claims 1-18 are rejected under 35 USC 102(e) as being anticipated by Krieg *et al.* (US Pat No. 6,207,646), Krieg (US Pat No. 6,218,371), or Krieg (US 6,429,199).

The essential feature of the presently pending claims is that any cationic lipid including can be used for a method of inducing an immune response against a tumor antigen present in a tumor bearing mammal when used in combination with a nucleic acid polymer including those non-expressible DNA containing CpG motifs nucleic acids, which themselves are also immunostimulatory nucleic acid molecules. Krieg *et al.* teach that cationic lipid carriers (The '646 patent, column 12, lines 25-34; the '371 patent, column 23 bridging column 24, column 24 second full par; the '199 patent, column 14 bridging column 15) can be employed in combination with a CpG motif containing non-expressible plasmid-derived (bacterial derived plasmid) nucleic acid polymer as immunostimulatory nucleic acid complex (the ' 646 patent, column 12, lines 12-24, lines 49-50; the '371 patent, column 22, lines 15-17, lines 43-67, column 24, second full par., column 30, lines 15-18; the '199 patent, column 14, lines 48-53, column 22, lines 14-18); when employed for induction of an immune response to a target cancer antigen (the '646 patent, column 6, lines 55-56, column 10, lines 16-23 ; the '371 patent, column 7; the '199 patent, column 10, lines 27-31). The '646 patent teach the same throughout the disclosure (particularly columns 29-35, columns 61-64). Intravenous administration of the CpG containing nucleic acid polymer complexed with a deliver carrier such as a cationic lipid is also disclosed (the '646 patent, column 34, line 53; the '371 patent, column 31, last paragraph; the '199 patent, column 25, lines 36-38.

Absent evidence to the contrary, the compositions and the methods disclosed in Krieg *et al.* have all of the properties cite in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-18 are rejected under 35 USC 103 as being unpatentable over Erabacher (US 2001, 0048939 A1) taken with the '646 patent, the '341 patent, or the '199 patent.

Erabacher teaches a method of employing a cationic lipid complex composed mainly of a cytofectin-based cationic lipid/CpG containing plasmid fragments for use in therapeutic vaccine (entire disclosure, particularly, page 4, par. 0090 and 0091. Intravenous administration of the

complex is disclosed on page 0102. Erabacher does not teach specifically that the complex can be used therapeutically against a tumor antigen in a tumor bearing mammal.

However, at the time the invention was made, the prior art exemplified by the '646 patent, the '341 patent, and the '199 patent does teach that CpG containing nucleic acid polymers alone or when complexed with a known pharmaceutically acceptable carrier such as cationic lipid is effective for use as a therapeutic vaccine against a tumor in a tumor bearing mammal (see the citations as indicated above).

It would have been obvious for one of ordinary skill in the art, on teachings provided by the combined cited references, to employ a cationic lipid complex composed mainly of a cytofectin-based cationic lipid/CpG containing plasmid fragments for use in therapeutic vaccine against a tumor antigen in a tumor bearing tumor.

One of ordinary skill in the art would have been motivated to employ the lipid/CpG containing bacterial derived plasmid to combat or inhibit a tumor growth in a tumor bearing mammal because the prior art exemplified by the '646 patent, the '341 patent, and the '199 patent does teach that CpG containing nucleic acid polymers alone or when complexed with a known pharmaceutically acceptable carrier such as cationic lipid is effective for use as a therapeutic vaccine against a tumor in a tumor bearing mammal.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claim 19 is free of the prior art of record because while the prior art of record exemplified by Harris (US Pat No. 5,650,096) teaches that the compound GL-67 is an effective cationic lipid carrier of a biologically active molecule, no single prior art of record teaches a therapeutic

composition comprising a non-expressible, CpG motif containing DNA. While one of ordinary skill in the art, on the basis of teachings provided by the totality of prior art of record, may have been motivated to employ the GL-67 compound as a matter of design choice or equivalency to enhance the delivery of a biologically active molecule *in vivo*, such motivation or suggestion is not sufficient to overcome the surprising results as shown throughout the working examples provided by the specification: GL-67 not only acts a carrier of a non-expressible, CpG motif containing DNA, the compound also unexpectedly enhances the survival of the treated tumor established animal models.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Please note that the examiner is expected to move to a new US PTO office building located in Alexandria on January 12, 2004. The examiner office phone number at the new building is **571-272-0731.**

Dave Nguyen
Primary Examiner
Art Unit: 1632